

Infective endocarditis

An African experience

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A two-year review of 102 consecutive cases of infective endocarditis is presented from Uganda. Fifty-seven patients were diagnosed at clinical presentation and 45 were diagnosed only at necropsy. The majority of patients clinically presenting with infective endocarditis had underlying rheumatic heart disease, with staphylococci and streptococci the commonest infecting organisms. On adequate antibiotic therapy the mortality was 19 per cent. The majority of those diagnosed at necropsy presented an acute course with rapid termination in cardiac failure, frequently due to acute valvular destruction in the absence of pre-existing valvular disease. These experiences in a developing country are different from the spectrum of infective endocarditis as seen at present in western countries.

Studies of infective endocarditis in African populations are few. Necropsy surveys from Uganda (Davies, 1948) mentioned the frequent occurrence of acute bacterial endocarditis of the aortic valve in the absence of antecedent heart disease. Subacute bacterial endocarditis complicating rheumatic heart disease was stated to be uncommon. In a clinical report (D'Arbela, Kanyerezi, and Tulloch, 1966), bacterial endocarditis accounted for 2.2 per cent of all cardiovascular admissions. A short clinical report of bacterial endocarditis in Uganda was made by Brenton *et al.* (1968).

The present study was undertaken to define the pattern of infective endocarditis at Mulago Hospital. The aims were to assess clinical presentation, sources of infection, causative organisms, and prognosis, and to compare the findings with current experience in western countries.

Subjects and methods

Each patient admitted to Mulago Hospital between January 1968 and December 1969 with the clinical diagnosis of infective endocarditis was

seen by one of us. The clinical presentation and reasons for diagnosis were documented. The investigation and management of the patients conformed to a standard routine. Three to 6 blood samples of 3 to 5 ml each were taken for culture by the house staff within a few hours of admission in most instances and sent to the routine bacteriology diagnostic service of the hospital. Arbitrary treatment was started on strong clinical suspicion as soon as the blood cultures had been taken. Each sample of blood was inoculated into bottles containing 10 ml 0.5 per cent 'liquoid' (sodium polyanetholsulphonate) broth. The bottles were incubated aerobically overnight at 37°C and subcultures were made on human blood agar after 24 hours, 48 hours, and 1 week of incubation. Additional bile broth inoculation was done in the majority of the patients and subcultures were made on MacConkey media at 24 and 48 hours. During the same two-year period, all cases of infective endocarditis diagnosed at necropsy were scrutinized for clinical details and pathological findings.

Data on a total of 102 consecutive cases of infective endocarditis seen over a 24-month period are included in this study. The patients were divided into 2 groups for analysis. In Group 1, consisting of 57 patients with a clinical diagnosis, there were 33 in whom the diagnosis of bacterial endocarditis was proved on blood culture; 8 of these patients died and 3 were followed to necropsy. In 24 cases in whom blood cultures were negative, the diagnosis of infective endocarditis was strongly suggested by the presence of cardiac murmurs together with fever, splenomegaly, finger-clubbing, or embolic manifestations. These patients were treated for bacterial endocarditis;

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there were 3 deaths and 1 necropsy. Group 2 consisted of 45 cases in whom a substantive diagnosis of infective endocarditis was made only at necropsy.

Results

Age and sex incidence Of the 96 patients whose ages were known, 66 were less than 40 years old (Fig.). The male-to-female ratio was 2:1 for the group as a whole. The ratio was almost equal in the younger age groups; in the older age groups, however, almost all the patients were male. The male to female ratio of admissions in the medical wards of Mulago Hospital is 1:1.

Underlying heart disease The aetiology of the underlying heart disease where it was determined is shown in Table 1. A preponderance of rheumatic heart disease, 37 cases (65%), was found in the clinically diagnosed series, Group 1. The majority were aortic incompetence and mitral incompetence (Table 2). The aortic and mitral valves were almost equally affected by endocarditis in the 15 cases (26%) with no previously suspected heart lesion.

In Group 2, who were diagnosed at necropsy, rheumatic heart disease occurred less frequently, 13 cases (29%). There were 25 cases (56%) with no obvious underlying heart disease and 3 with endomyocardial fibrosis. In the 25 cases with no previous heart disease the aortic valve alone was the seat of endocarditis in 18, the mitral alone in 4, and the tri-

TABLE 1 *Nature of underlying cardiac lesions in 102 cases of infective endocarditis.*

Heart lesion	Group 1 (clinical cases)		Group 2 (necropsy cases)	Total
	Bacteriology positive	Bacteriology negative		
Rheumatic	23	14	13	50
Congenital	1	3	4	8
Endomyocardial fibrosis	—	—	3	3
Calcific aortic sclerosis	1	—	—	1
No underlying heart lesion	8	7	25	40
Total	33	24	45	102

cuspid alone in 2. In 1 case both aortic and mitral valves were involved.

Congenital heart disease was represented in small numbers in both the clinically diagnosed and the necropsy groups. No cases were related to cardiac surgery.

Presenting symptoms and signs

Clinically diagnosed series (Group 1) An analysis of the clinical presentation of the patients with a proved or presumptive diagnosis of bacterial endocarditis is shown in Table 3. Fever, heart failure, malaise, and embolic episodes were common presenting features. Evidence of underlying cardiac disease, usually rheumatic heart disease, was common.

Necropsy series (Group 2) In two-thirds infective endocarditis was not suspected in life. In the few in whom it was considered, the patients died before the diagnosis could be confirmed. Only 10 of the 45 cases had peripheral manifestations such as finger-clubbing, splinter haemorrhages, and subconjunctival haemorrhage to suggest infective endocarditis.

Congestive cardiac failure had been the most common clinical presentation. Fever had been noted during life in just over half the patients. Neurological manifestations were present in 16 patients of whom 9 had a meningitic picture, 4 had hemiplegia, 2 were in

FIG. *Age distribution of 96 cases of infective endocarditis. In 6 adult cases the age was not recorded.*

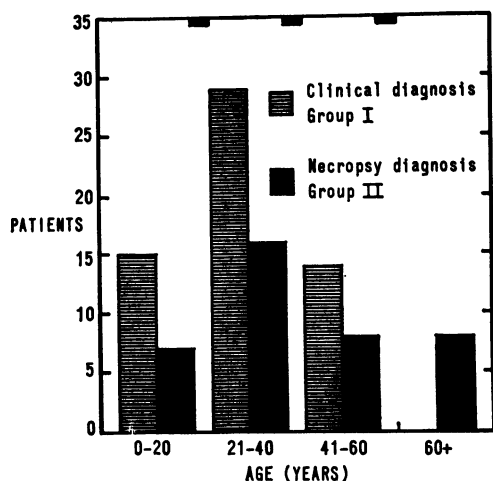


TABLE 2 *Diagnosis in 37 patients with rheumatic heart disease and infective endocarditis (Group 1)*

Diagnosis	No.
Mitral incompetence	13
Mitral stenosis and incompetence	2
Mitral incompetence and aortic incompetence	14
Aortic incompetence	8
	37

TABLE 3 Clinical features of 57 patients with infective endocarditis (Group 1)

Presenting symptoms	No.	Per cent
Fever	46	(81)
Cardiac failure	29	(51)
Malaise	24	(42)
Embolic episodes	17	(30)
Principal findings		
General		
Cardiac murmur	42	(74)
Finger clubbing	29	(51)
Splenomegaly	23	(40)
Jaundice	7	(12)
Haematological findings		
Raised erythrocyte sedimentation rate	31	(55)
Anaemia	24	(42)
Leucocytosis	21	(37)
Haemorrhagic phenomena		
Microscopical haematuria	17	(30)
Splinter haemorrhages	7	(12)
Petechial haemorrhages (including retinal haemorrhages)	4	(7)
Subconjunctival haemorrhages	2	(4)

deep coma, and 1 presented in a confusional state.

The duration of illness as given in the history was less than one week in about a quarter of the patients and 1 to 4 weeks in about half the patients. A quarter of the patients were moribund, and gave no history. Sixteen patients died on the day of admission, and 13 within 7 days.

Bacteriology Positive blood cultures were obtained in 38 cases: 5 of them were from the necropsy series (Group 2) in which the results became available only after the patient's death (Table 4). From the rheumatic cases, staphylococci and streptococci were isolated with equal frequency. In those with no under-

lying heart disease *Staph. aureus* was more common.

There were 2 patients with *Klebsiella* endocarditis and both had mixed infections. One presented with *Klebsiella* septicaemia following urethral bouginage for stricture. A mitral systolic murmur and systemic embolization to the toes with gangrene were noted. Two weeks later *Strep. faecalis* was isolated from the blood and urine. Another presented with *Staph. aureus* endocarditis and subsequently *klebsiella* was cultured from the blood and urine.

Bacteriological studies of a necropsy series seen over a confined 12-month period will be described elsewhere (Steiner *et al.*, 1972).

Source of bacterial infection The focus of infection giving rise to the endocarditis was evident in only 38 of the total 102 cases. The apparent sources of infection in the clinically diagnosed and necropsy groups were similar and are shown in Table 5. The teeth and gums of most of the patients appeared unremarkable.

Treatment programme Of 12 cases of *Staph. aureus* infection in which full sensitivity results were obtainable, 10 were penicillin resistant, 5 streptomycin resistant, and 8 tetracycline resistant; 4 cases were penicillin and streptomycin resistant and 2 were resistant to all 4 antibiotics. The majority of the streptococci isolated were sensitive either to penicillin or streptomycin or both.

Pending the results of cultures and in all cases in which they proved negative, the treatment consisted of crystalline penicillin and streptomycin usually by intermittent intramuscular injection. The standard regimen was crystalline penicillin 16 to 40 mega units and streptomycin 1 g intramuscularly daily for a period of 4 to 6 weeks. Where high concentrations of penicillin were needed in cases of bacterial resistance, massive doses, up to 40

TABLE 4 Causative micro-organism in 38* patients with bacteriologically proven endocarditis

<i>Staph. aureus</i>	16†
<i>Staph. albus</i>	4
<i>Strep. viridans</i>	9
<i>Strep. faecalis</i>	2†
<i>Strep.</i> (unidentified)	2
<i>Escherichia coli</i>	2
<i>Pneumococcus</i>	2
<i>Pseudomonas</i>	1

* Includes 5 necropsy cases (Group 2) in which bacteriology results became available after death.

† One case each had mixed infection with *klebsiella*.

TABLE 5 Apparent source of infection in 102 cases of infective endocarditis

Respiratory	16
Gynaecological	5
Urinary tract	5
Septicaemia	5
Skin sepsis	3
Panophthalmitis	1
Dental	3
Not evident	64
Total	102

million units per day, were given by intermittent 6-hourly intravenous infusion. We encountered no cases of allergy to penicillin. Probenecid was employed infrequently. In one patient infected with a resistant *Strep. faecalis*, chloramphenicol was used in addition to penicillin and streptomycin. In 4 patients infected with strains of *Staph. aureus* resistant to penicillin and streptomycin, the drugs used were trimethoprim and sulphamethoxazole, chloramphenicol, lincomycin, and vancomycin. Gentamicin in combination with crystalline penicillin was used in the 2 cases of klebsiella endocarditis. Selection and combination of antibiotics used depended on their availability in our hospital at the time.

Prognosis in clinical bacterial endocarditis (Group I) Of the 57 patients diagnosed and treated for infective endocarditis, 11 died (19%). Necropsy was performed in 4 cases and the diagnosis confirmed. Unremitting congestive cardiac failure (7 cases) and cerebral embolism (2 cases) were the usual fatal events. One patient committed suicide while under treatment. Pre-existing valve damage and worsening of the haemodynamic effects after healing largely determine the prognosis of the surviving patients.

Causes of death in infective endocarditis diagnosed at necropsy (Group II) Congestive cardiac failure was the most common cause of death. Rupture or perforation of the aortic or mitral valve was frequent (16 and 8 cases, respectively). A cerebrovascular accident led to death in 13 patients. Other factors contributing to death were pneumonia, ruptured spleen, and uraemia. A patient with pulmonary tuberculosis died from massive haemoptysis.

Gross underlying systemic disease, chronic pulmonary suppurative disease, and hepatic cirrhosis were also seen at necropsy and may have contributed to death in individual patients. The detailed pathology of the necropsy cases will be described elsewhere (Steiner *et al.*, 1972).

Discussion

There have been several recent reports on the changing pattern of infective endocarditis in western countries in the past 20 years (Lancet, 1967; British Medical Journal, 1969). Notable features have been a real increase in incidence among elderly male patients with no clear antecedent heart disease, and infection with organisms less manageable than *Strep. viridans* (Hughes and Gauld, 1966). The overall mortality is apparently unaltered

despite advances in chemotherapy. In Kampala, the incidence of endocarditis without antecedent heart disease as shown in this report is high, being 26 per cent in those diagnosed clinically and 56 per cent in those in whom the diagnosis was established at necropsy. However, there was no particular predilection for the elderly, and cases were found in all age groups. It is clearly proven also in Kampala (Steiner *et al.*, 1972) that infection can occur on the normal endocardium as has been reported elsewhere (Pankey, 1961; Vogler, Dorney, and Bridges, 1962).

An apparent change compared with previous experience at this hospital (Davies, 1948) has been a conspicuous increase in infective endocarditis in patients with rheumatic heart disease. This may be due in part to increased clinical awareness of rheumatic heart disease, which accounts for about 30 per cent of all patients with heart disease attending the Cardiac Clinic at Mulago Hospital (Somers, D'Arbela, and Patel, 1972). In the patients with chronic rheumatic heart disease, with infection due to *Staph. aureus* and *Strep. viridans*, the clinical presentation resembled closely the classical pattern of infective endocarditis of the older reports in the preantibiotic and the early antibiotic era (Cates and Christie, 1951). Established heart disease or a cardiac murmur, together with fever, finger-clubbing, embolic phenomena, and splenomegaly were the common features drawing attention to the diagnosis of infective endocarditis. Clubbing was present in half the cases, contrasting with the low incidence (13%) reported by Lerner and Weinstein (1966) in the United States. On the other hand we were unable to achieve, due presumably to faulty technique, the 37 to 93 per cent finding of haematuria cited by the American workers. There was no evidence in our series of Osler's nodes, Janeway lesions, or a skin rash.

Of the cases diagnosed for the first time at necropsy, the duration of illness was usually very short. The patients were acutely ill and the majority died on the day of admission or within one week. Evidence of cerebral emboli and perforation of infected valves was common. There were hardly any patients with atherosclerotic heart disease as notable in western countries (Uwaydah and Weinberg, 1965; Hughes and Gauld, 1966). This is in keeping with the relative infrequency of atherosclerotic heart disease in Africans and the younger age of the community from which the patients came.

Since the introduction of antibiotics there has been a fall in the incidence of endocarditis caused by *Strep. viridans* in western countries

(Lerner and Weinstein, 1966). At the same time, there has been an increase in infections due to *Strep. faecalis*, *Staph. aureus*, and less common organisms. This trend is also evident in this study where *Staph. aureus* was the single most common organism isolated. In the 5 bacteriologically proven cases studied by Brenton *et al.* (1968) in Kampala, there was only one patient infected with *Strep. viridans*. Unusual organisms they encountered were *Haemophilus para-influenzae*, *Pasteurella multocida*, and a nonhaemolytic streptococcus.

Blood cultures were negative in 42 per cent of the patients with a clinical diagnosis of infective endocarditis in this study. Various factors responsible for failure to recover organisms in cases of bacterial endocarditis have been pointed out (Lerner and Weinstein, 1966; Shinebourne *et al.*, 1969). Of these, the prior use of antibiotics and faults in the technique of blood collection and culture are the most important. Mulago Hospital is the central referral hospital for patients from nearby dispensaries and upcountry hospitals. Many patients had some form of antibiotic treatment, either before referral or in the admitting service of the hospital, before blood cultures were taken. Brenton *et al.* (1968) showed that precise diagnosis of bacterial endocarditis can be achieved in most patients by means of meticulous culture techniques, with adequate numbers of blood samples and minor modification of laboratory methods. A few of our bacteriologically negative cases might have proved to be due to anaerobic organisms had it been possible to culture for them routinely.

In just over a third of the cases the source of infection was shown either in life or at necropsy. Respiratory, gynaecological, and urinary tract infection, often after instrumentation, and septicaemia were the apparent sources of infection. It was in only 3 patients that a history of dental treatment preceding the endocarditis was obtained. The generally healthy state of the teeth and the rarity of dental manipulation in the Ugandan population may explain the low prevalence of a dental source of endocarditis.

Among the patients treated for infective endocarditis the immediate mortality rate compares favourably with that recorded elsewhere (Shinebourne *et al.*, 1969). Some of the deaths due to perforated valves might have been deferred if the diagnosis had been suspected early and vigorous antibiotic therapy instituted. Facilities for valve repair or valve replacement in Uganda would have helped the longer term prognosis in those with valve

destruction and intractable cardiac failure. In occasional cases underlying systemic disease may have contributed to mortality. We encountered no cases of malignant disease.

Ziment (1969) has shown that the incidence of neurological complications of bacterial endocarditis has remained unchanged in spite of the introduction of antibiotics. In our experience neurological complications, especially meningitis and cerebral embolism resulting in hemiplegia, were common, and contributed directly or indirectly to death in a substantial number of patients. In the majority of patients the illness was thought to result from a primary neurological disorder, and the presence of bacterial endocarditis was missed completely. Ziment further notes that failure to recognize underlying bacterial endocarditis in patients presenting with a neurological complaint often leads to a fatal outcome. Patients with a neurological manifestation have a higher mortality than those without it (Jones, Siekert, and Geraci, 1969).

It is apparent from this study that a classification of infective endocarditis into those with an acute course and those with a subacute course is valid. The differentiation of 'acute' from 'subacute' depends upon the virulence of the infecting organism, the severity and rate of progression of the disease, and whether or not the aortic valve is destroyed. We believe with Uwaydah and Weinberg (1965) that distinguishing between the 2 forms is useful prognostically and emphasizes the necessity for rapid institution of intensive therapy in acute cases if survival is to be improved.

Although the findings in this study refer to only one part of Africa we believe that experiences will be similar in most developing countries in Africa and Asia.

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